Asymmetric transfer hydrogenation: chiral ligands and applications

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Received 26th October 2005
First published as an Advance Article on the web 19th December 2005
DOI: 10.1039/b513396c

Hydrogen transfer reduction processes are attracting increasing interest from synthetic chemists in view of their operational simplicity and high selectivity. In this *tutorial review* the most significant advances recently achieved in the stereoselective reduction of unsaturated organic compounds catalyzed by homogeneous transition metal complexes are critically reviewed. A sharp growth of the synthetic applications of this technique in the synthesis of fine chemicals is predictable as the use of transition metal catalyzed reactions will become more familiar to synthetic chemists.

Introduction

The asymmetric reduction of unsaturated compounds provides good opportunities for the simultaneous introduction of new functionalities and new stereogenic elements into the structure of organic compounds. For this reason this process has become one of the most popular tools in asymmetric synthesis and has been exploited in the preparation of a variety of organic products of biological interest featuring diverse functional groups.

Among the methodologies presently amenable for this purpose, H-transfer reduction[1] (Scheme 1) has gained in recent years a prominent position as to be rated second in order of importance immediately behind asymmetric hydrogenation with molecular hydrogen. The increasing success of this technique follows from its operational simplicity and reduction of the risks associated with the use of an easily inflammable gas of high diffusibility.

These intense research efforts have resulted in significant advances in the development of new catalysts of higher activity/selectivity; in the understanding of the reaction mechanisms, particularly as to the Ru-catalyzed reactions; in exploring unconventional approaches driven by green

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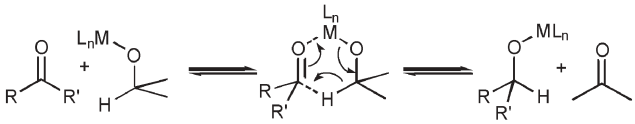
Serafino Gladiali

Prof. Serafino Gladiali was born in Milan. He accomplished his studies in Industrial Chemistry at the University of Milan where he received the ''Laurea'' in Industrial Chemistry in 1968. After gaining four years experience in industrial research on steroid chemistry, in 1972 he accepted a position at the University of Sassari, where he is now full Professor of Industrial Organic Chemistry at the Faculty of Sciences. His main research interests are centred on asymmetric homogeneous catalysis and ligand design. Stereoselective synthesis of optically active organic compounds, mainly nitrogen heterocycles and atropisomeric phosphorus and sulfur derivatives is a further area of his research. He has co-authored over 200 papers, patents and communications covering the areas of enantioselective hydroformylation and hydrogen transfer reduction; synthesis and applications to asymmetric catalysis of chiral heterocycles with pyridine nitrogen donors; preparation and catalytic applications of atropisomeric phosphorus and sulfur donor ligands; application of enantioselective catalysis to the synthesis of chiral molecules of biological interest.

Elisabetta Alberico

Elisabetta Alberico was born in Ferrara, Italy, in 1965. She obtained her degree in Chemistry (Laurea) from the University of Sassari in 1993. From 1993 to 1996 she worked at the University of Sassari in Prof. Gladiali's group and for the National Research Council as research assistant in the field of asymmetric homogeneous catalysis. After spending ten months at the University of Ottawa in 1998 in the group of Prof. Howard Alper, she moved to the Rheinisch-Westfälische Technische Hochschule where she obtained her PhD under the supervision of Prof. Albrecht Salzer. Since 2001 she has held a permanent position as researcher at the Institute of Biomolecular Chemistry of the National Research Council in Sassari. Her research interests are in the fields of organometallic chemistry, asymmetric homogeneous catalysis and application of catalytic methods to the synthesis of molecules endowed with biological activity.

Scheme 1



Scheme 2 Direct H-transfer: metal-templated concerted process.

chemistry principles; in exploiting the potentiality of transition metal-enzyme coupled catalysis in dynamic kinetic resolution (DKR) processes.

Mechanisms

Hydride transfer from the H-donor $\mathbf{DH_2}$ to the substrate **A** (Scheme 1) can take place according to two limiting mechanisms: a metal-templated concerted process (*direct H-transfer*) or a metal hydride mediated multi-step process (*hydridic route*).[2]

The *direct H-transfer* (Scheme 2) proceeds *via* a complex in which both the donor and the acceptor are bound to the metal and are held in close proximity. Upon coordination to the metal, the substrate is activated towards the nucleophilic attack of the hydride. The metal acts as a template providing the reactants with the correct orientation for a concerted shift of hydride to be feasible. A cyclic transition state like the one proposed for the Meerwein–Ponndorf–Verley reaction is possibly involved. This mechanism is typical of, albeit not restricted to, non-transition metals.

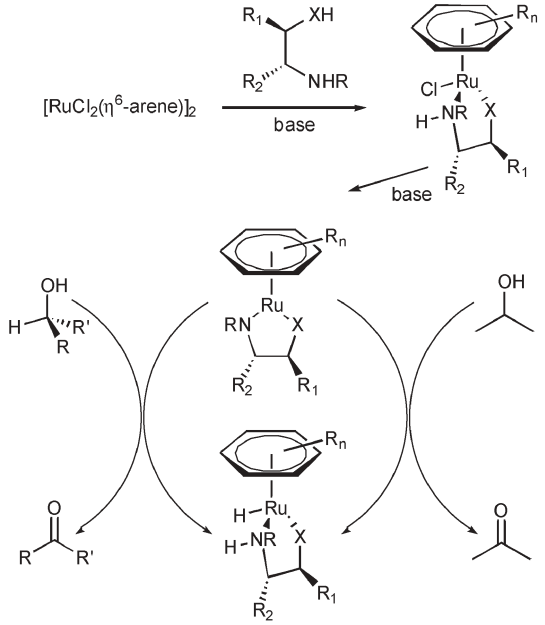
The *hydridic route* involves the intermediate formation of a discrete metal hydride by interaction of the catalyst with the H-donor, followed by hydride transfer from the metal hydride to the substrate. Thus, the donor and the acceptor interact separately with the metal at different stages of the reaction. Transition metals most commonly promote the hydridic mechanism.

Depending on the ligand coordinated to the metal, either a *mono-* (Scheme 3) or a *dihydride metal species* (Scheme 4) may be involved. The substrate may be directly coordinated to the metal (*inner sphere* mechanism, Scheme 4) or may slip into the chiral pocket of the complex thanks to a cooperative process involving hydrogen bonds and dipolar interactions of the functional group with different sites of the catalyst (*metal–ligand bifunctional catalysis*, *outer sphere* mechanism, Scheme 3).[3] These mechanisms are dealt with in detail in the next review[2b] of this issue.

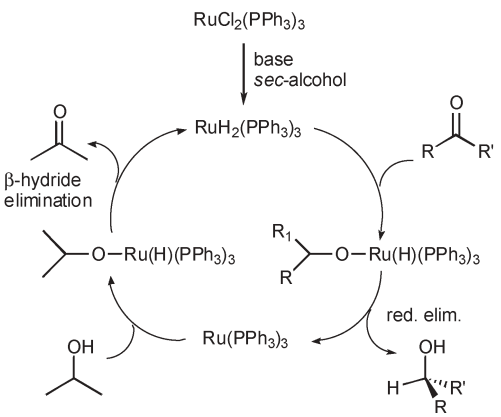
Hydrogen donors and promoters

Isopropanol (IPA) and formic acid/triethylamine (TEAF) are by far the most used sources of hydrogen in transfer hydrogenation.

During the process, IPA is oxidized to acetone (Scheme 5, **a**). This makes the reduction of ketones by IPA a reversible process where the equilibrium is regulated by the oxidation potentials of the relevant carbinol/ketone couples. To shift the

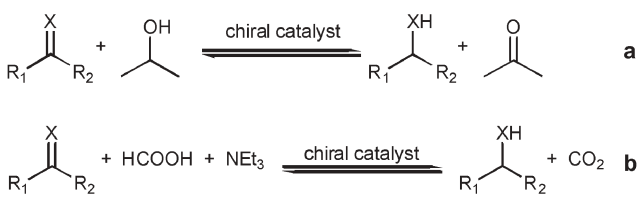


Scheme 3 Catalytic cycle of Ru-monohydride mediated H-transfer *via* metal–ligand bifunctional catalysis (*outer sphere mechanism*).



Scheme 4 Catalytic cycle of Ru-dihydride mediated H-transfer (*inner sphere mechanism*).

equilibrium towards the desired product, IPA is most frequently used as the solvent of the reaction. As the life-time of many metal catalysts in IPA solution is usually reasonably long even at reflux temperature, this allows for most reactions to be driven to high conversions. When IPA is the H-donor a base is usually required for the activation of the starting



Scheme 5 Sources of hydrogen: IPA (a) and TEAF (b) systems.

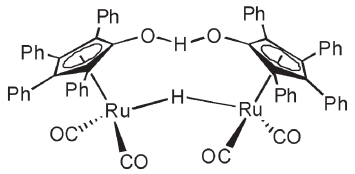


Fig. 1 Shvo catalyst.

complex to catalysis. Sodium or potassium carbonates, hydroxides or alkoxides at various concentration have been employed for this purpose. Quite few catalytic precursors do not require any base (Shvo catalyst, Fig. 1)[2a] or need just two equivalents for metal atom (Noyori's and similar catalysts).[3]

Although IPA is environmentally friendly and easy to handle, the reversibility of the reaction remains a major drawback in asymmetric H-transfer. At low conversions the reaction is kinetically controlled and the stereoselectivity may be high. As the conversion increases, the rate of the reverse reaction becomes higher and the ratio of enantiomers falls under thermodynamic control with gradual erosion of the enantiomeric purity of the product. This limitation can be overcome by continuously distilling off acetone as soon as it is formed or by operating in dilute solution.

Formic acid and its salts are better suited H-donors than IPA because their dehydrogenation in open systems is substantially irreversible due to the evolution of CO_2 (Scheme 5, **b**).[4]

An azeotropic 5 : 2 mixture of HCOOH and NEt_3 (TEAF) is most frequently employed as reducing agent. This gives a single phase at room temperature; it is miscible with many solvents at 20–60 °C; it allows for high substrate concentrations and brings about high conversions without back-reaction and racemization.

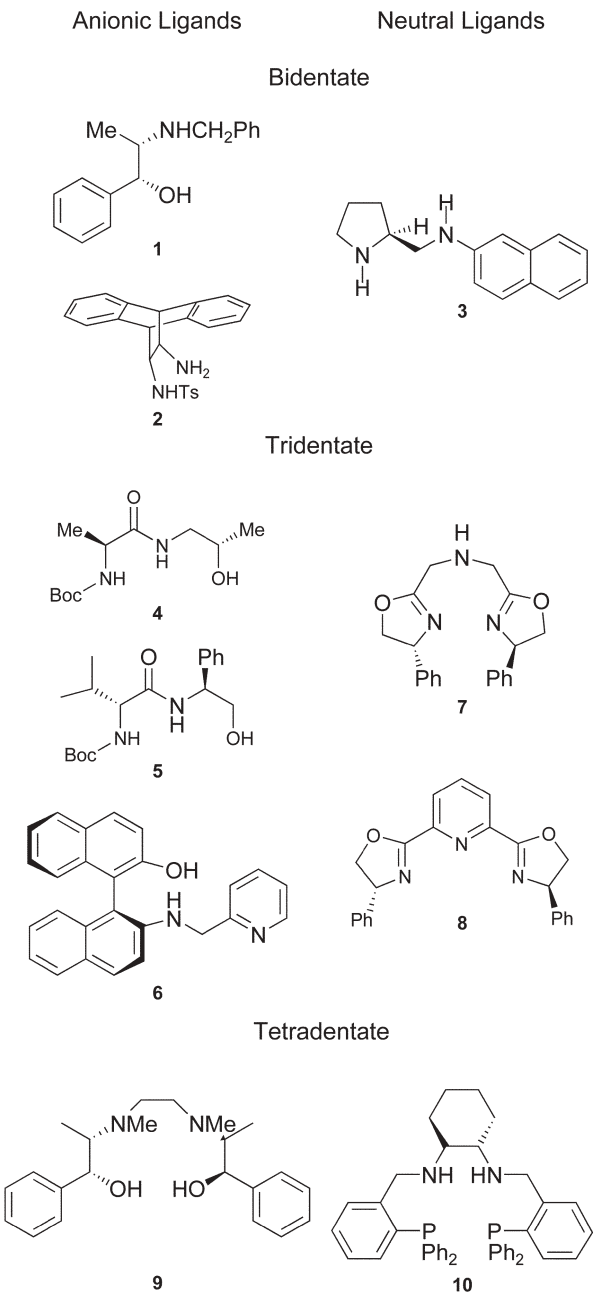
There are, however, some restrictions to the use of TEAF. Several complexes undergo fast decomposition on attempted dissolution in formic acid and some other ones lose completely their catalytic activity, probably because the acid inhibites one of the steps of the activation process promoted by the base.

Ligands

An exhaustive overview of the chiral ligands designed and applied to transfer hydrogenation is beyond the objective of this review. The ligands used in asymmetric H-transfer feature various combinations of nitrogen, oxygen, phosphorus, sulfur and even arsenic as the donor atoms. They can be bidentate, tridentate and tetradentate. Scheme 6 collects selected ligands which have provided enantioselectivities of practical significance (ee > 90%) in the reduction of acetophenone.[1a,5–7]

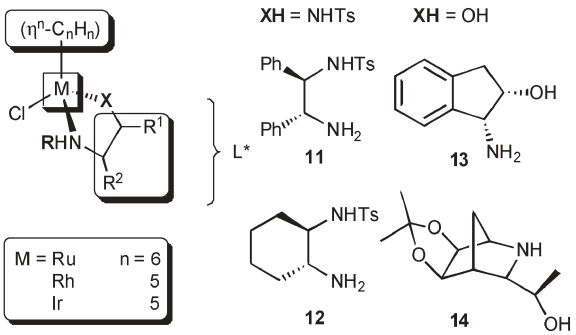
More appropriately ligands can be classified as anionic or neutral, depending on whether or not they possess a protonated donor centre –XH of appropriate acidity. This feature has important bearings as to the mechanism of transfer hydrogenation.

Among the potentially anionic ligands tested, the most effective, both in terms of catalyst performance (activity and enantioselectivity) and substrate scope, are 1,2-amino alcohols and monotosylated diamine (Scheme 7) and some phosphine-oxazoline derivatives such as **15** (Fig. 2). Half-sandwich

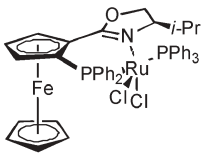


Scheme 6 Selected ligands which have provided ee ⩾ 90% in the reduction of acetophenone.[1a,5–7]

π-complexes, such as Ru–arene and Rh– or Ir–cyclopentadienyl complexes, are the most proper metal fragment to be associated to 1,2-amino alcohols and to monotosylated diamine ligands. Noyori's complex (Scheme 7: XH = –NHTos, ligand **11**, M = Ru, *n* = 6) seems to be the catalyst with the broadest scope as it provides significant ee's with a large variety of substrates. When $[RuCl_2(\eta^6\text{-arene})]_2$ complexes are employed as precatalysts with protic ligands, "metal–ligand bifunctional catalysis" is expected to operate.[3] Albeit less stringent than the anionic ligand, the η^6-arene fragment contributes significantly to the performance of these catalysts through a $C(sp^2)H/\pi$ interaction stabilizing the



Scheme 7 Privileged ligands for asymmetric H-transfer.



15

Fig. 2 Privileged catalyst precursor for asymmetric H-transfer of dialkyl ketones.

transition state (Fig. 3, **a**). Polyalkylated arenes of increasing steric demand generally provide higher ee's than the unsubstituted counterparts, even if at the expense of reactivity. This has been ascribed to an improved stabilization of the transition state due to the increased π-donation of the arene and/or to the contribution of an attractive secondary $C(sp^3)H/\pi$ interaction (Fig. 3, **b**).

A clue into the structural factors which root the remarkable enantiocontrol of Noyori's catalyst in the transfer hydrogenation of ketones has been recently provided by Wills (Scheme 8).[8a] In a comparative trial, the four monotosylated diamines of related stereochemistry **11**, **16**, **17** and **18** have been inspected for their efficiency as chiral inducers in the hydrogen transfer reduction of acetophenone. The ligands with only one stereocentre (**17** and **18**) afford the alcohol with the

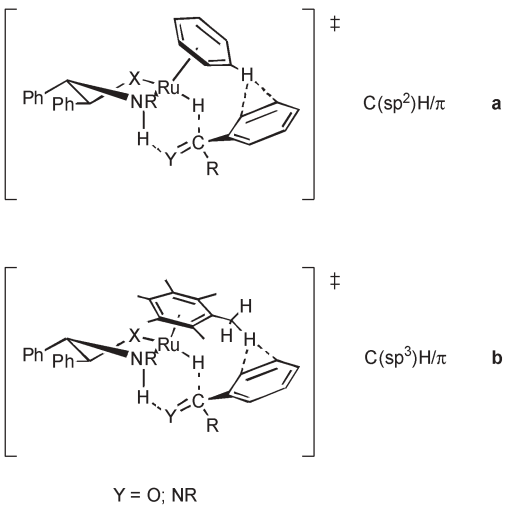
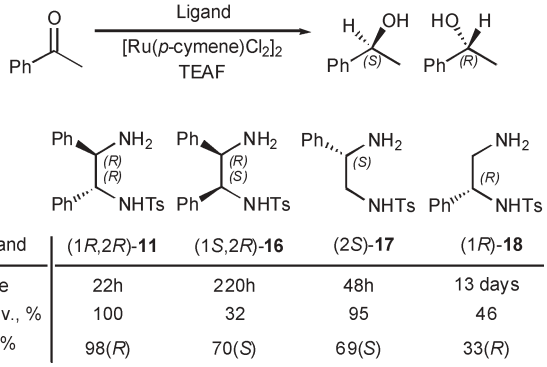


Fig. 3 Transition state for Ru-monohydride mediated H-transfer *via* metal–ligand bifunctional catalysis (*outer sphere mechanism*).



Ligand	(1*R*,2*R*)-**11**	(1*S*,2*R*)-**16**	(2*S*)-**17**	(1*R*)-**18**
Time	22h	220h	48h	13 days
Conv., %	100	32	95	46
Ee, %	98(*R*)	70(*S*)	69(*S*)	33(*R*)

Scheme 8 Results obtained in the transfer hydrogenation of acetophenone using Noyori's and related tosyldiamines.

same configuration as the inducing ligand. With the ligands containing two stereocentres (**11** and **16**), the configuration of the alcohol follows from the stereochemistry of the carbon bound to the tosylamine. Thus, the handness of the product is dictated by the absolute configuration of this centre and a matched combination of the two stereogenic centres is required for a high stereoselectivity to be attained. The *trans* orientation of the substituents on C(1) and C(2) provides both for an improved stereocontrol and for a higher reaction rate.[8b–d]

As a general trend, in the case of ruthenium, chiral 1,2-amino alcohols (Scheme 7, ligands **13** and **14**) provide the catalysts featuring among the highest activities in IPA. Their activity, however, is completely inhibited by formic acid, probably because deprotonation of the hydroxyl group is completely suppressed. At variance, the Ru-complexes derived from monotosylated diamine ligands are catalytically active even in TEAF.

Among the most recent and successful evolutions of this structural motif are the *tethered* ruthenium catalysts **19** and **20** (Fig. 4) in which the monotosylated diamine has been covalently bound to the η^6-arene group.[9] The tether was conceived in order to achieve an improved enantiocontrol by locking the chiral elements of the ligand and the η^6-aryl group in the best conformation for the transition state. Moreover, the longevity of the catalyst benefits from the "three-point" ligand attachment to the metal.

Both complexes have proved as enantioselective as the untethered counterpart. Complex **20**, in which the tether has been attached to the amino group, displays a catalytic activity higher than both **19** and the untethered one and can be used at loadings as low as 0.01% mol.

Recently it has been shown that ruthenacycles arising from cyclometalation of primary and secondary amines are effective

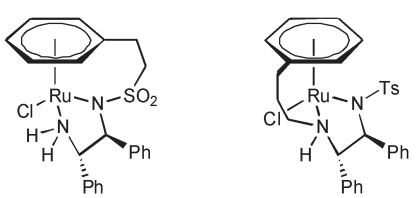
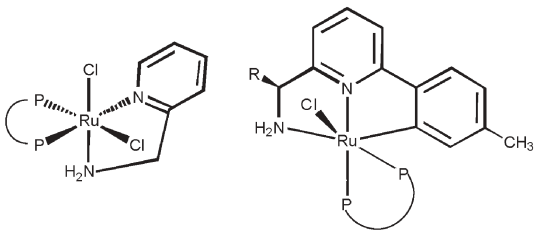


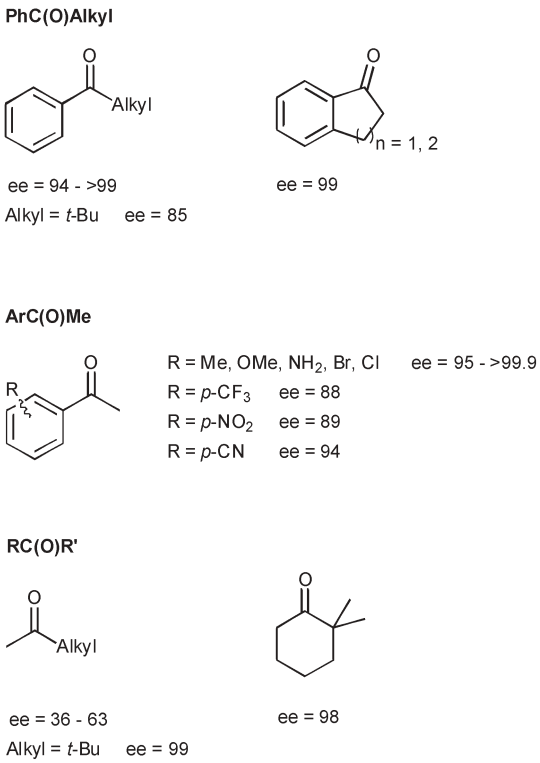
Fig. 4 Tethered ruthenium catalysts.



21 **22a** R = H **22b** R = *t*-Bu

Fig. 5 Ru(II) catalysts of superlative activity.

catalysts for asymmetric transfer hydrogenation.[10a] Ru(II)-catalysts of superlative activity (TOF over 10^5 h^{-1}) are obtained by assembling in the same hexacoordinated complex (**21**) a chelating diphosphine with 2-aminomethyl pyridine.[10b] Notably, the TOF can be pushed even further (over 10^6 h^{-1}) by using 6-*p*-tolyl-2-aminomethyl pyridine as co-ligand.[10c] Due to orthometalation, this last ligand binds in pincer-like fashion providing for the equatorial C,N,N-terdentate coordination to the metal center (**22a**).[10c] The reduction of aryl alkyl ketones proceeds in high enantioselectivity (94% for **21** and 87% for **22b**) with no significant reduction of rate when a chiral diphosphine or a chiral pyridine are used as ligands. These results confirm previous findings[3,8d] on the synergic role of unsubstituted sp^3-nitrogen donors in this catalysis (''N–H'' effect)[1d] and provide the chance for exploiting the matching–mismatching pairing of chiral ligands.



Scheme 9 Ee values (%) obtained in the asymmetric transfer-hydrogenation of aryl alkyl ketones and dialkyl ketones.

Applications

Asymmetric synthesis

Reduction of C=O. Phenyl alkyl ketones **PhCOAlkyl** are the substrates of choice for the assessment of a new catalyst in transfer hydrogenation (Scheme 9). For a given catalytic system, rate and selectivity are sensitive to the steric crowding of the substrates as well as to the electronic properties of the phenyl ring substituents. Transfer hydrogenation of sterically hindered ketones is often associated with lower reaction rates and lower enantioselectivities. In the reduction of phenyl alkyl ketones, it has been sometimes observed that the carbinol arising from *tert*-butyl ketones has a comparable ee, but the opposite configuration compared to the products obtained from other phenyl alkyl ketones.[1a] Apparently, the steric bulk of the *tert*-butyl group forces the substrate to approach by the opposite face compared to other alkyl phenyl ketones. A flavour of these trends can be appreciated from Scheme 9 where the highest stereoselectivities obtained on a small range of representative ketones are collected.

It is more difficult to identify a rationale for enantioselectivity in the reduction of ring-substituted acetophenones **ArCOMe** with the privileged ligands (ee $\geqslant$ 95%) (Scheme 9). The presence of an electron-withdrawing group on the phenyl ring has generally been found to facilitate the hydrogen transfer reaction and this has been attributed to the hydridic nature of the reducing species involved. As such, owing to the fast hydride transfer, the reactions of $-CF_3$ substituted substrates should proceed at higher rate, while reactions with electron-donating substituents ($-OCH_3$ and $-CH_3$) should proceed in more controlled manner. This behaviour, however, is not always observed. Depending on the substrate, different catalysts are required for the best matching of yield and enantioselectivity to be achieved.

In the presence of Noyori's catalyst (Scheme 7: **X** = –NHTos, ligand **11**, M = Ru, n = 6), a large variety of simple aryl alkyl ketones can be smoothly converted to the corresponding secondary alcohols at room temperature.[1c] The reduction can be run with both IPA and TEAF as hydrogen sources. Acetophenone and propiophenone are easily reduced with >97% optical yield, but the reaction of ketones having a bulky alkyl substituent is sluggish. Likewise, *ortho*-substituted acetophenones, such as *ortho*-tolyl methyl ketone, react slowly. Both 1′- and 2′-acetonaphthone are reduced with high enantioselectivity but at different rates, the latter being reduced much faster. 1-Indanone and 1-tetralone are also converted to the corresponding alcohols in high enantioselectivity, but in slightly lower yield. A *p*-methoxy group in acetophenone significantly decreases the enantioselectivity, whereas *m*-chloroacetophenone gives the best results, 98% yield and 98% ee. If the reduction is carried out in TEAF, the reduction of *p*-methoxyacetophenone improves substantially with 99% yield and 97% ee. The asymmetric reduction of 1-indanone and 1-tetralone is best effected in these conditions to give 1-indanol and 1-tetralol in 99% ee and more than 99% yield. Electron-withdrawing substituents in *para*-substituted acetophenones instead tend to slightly decrease the enantioselectivities.

The reduction of *m*-trifluoromethyl-acetophenone, a key step in the preparation of a commercial fungicide, can be performed in up to 100 kg batch scale using Noyori's catalyst and TEAF: at a substrate/metal ratio as high as 5000/1, the corresponding alcohol is obtained in 96% yield and 91% ee.[1a]

The catalyst developed by Andersson *et al.* based on Ru(II)-arene complexes containing 2-azanorbornyl alcohols as chiral ligands, is by now one of the most active and productive catalysts for the enantioselective transfer hydrogenation of a variety of aryl ketones. Optimization of the lead structure of the ligand by combined introduction of a dioxolane in the backbone and a methyl group in the α-position to the OH group (Scheme 7, ligand **14**), brings about the reduction of aromatic ketones that contain either electron-donating or electron-withdrawing substituents in *ortho*, *meta* and *para* positions with excellent enantioselectivities.[11] This catalyst, however, cannot be used in TEAF.

The reduction of selected dialkyl ketones **RCOR′** (Scheme 9), which are notoriously difficult to transform into the corresponding alcohols with high enantioselectivities, has been successfully achieved with the aid of Ru phosphino-oxazoline (*i*-Pr) catalysts **15** (Fig. 2). Over 99% ee's have been scored with *tert*-butyl methyl ketone and 2,2-dimethylcyclo-hexanone, albeit with moderate TONs and low TOFs.[1a] For methyl alkyl ketones, the enantioselective bias is clearly dependent on the bulkiness of the alkyl group: the bulkier the group, the higher the selectivity (*tert*-butyl > cyclohexyl > *n*-hexyl).

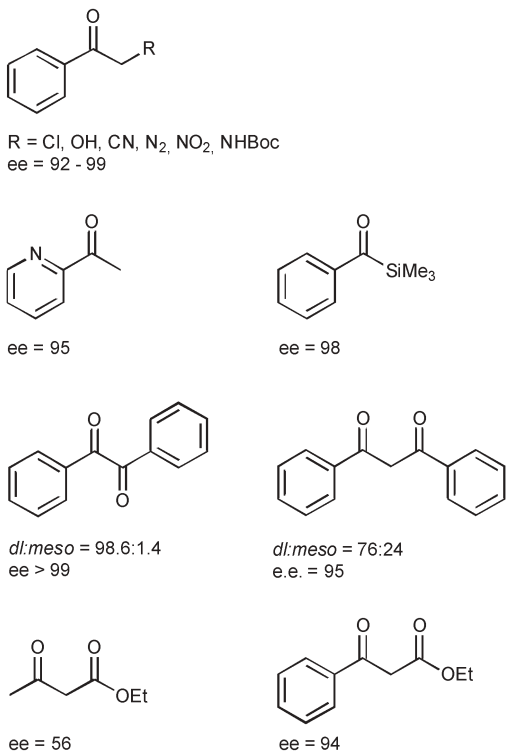
The asymmetric deuterohydrogenation of benzaldehydes **ArCHO** has been successfully accomplished in 98% ee with deuteroformic acid as the D-donor. Even if the synthetic scope of this reaction is modest, this is a real novelty because until recently H-transfer catalysts were unfit for the reduction of the formyl group. Stereoselectivities are lower with conjugated aldehydes and disappointingly poor with aliphatic substrates.[12]

The asymmetric transfer hydrogenation of ketones containing an additional functionality **ArCOX–RCOX** (Scheme 10) which might serve for the synthesis of more sophisticated products of interest in fine chemical industry has been achieved with ee ranging from 92% to more than 99%.

N-tosyl diamines complexes of Ru (but even of Rh and Ir) have confirmed their wide scope also in the reduction of bifunctional substrates. In this case Ru-complexes with amino alcohols and ephedrine-type ligands provide good performances as well, but with some limitations.

Optically active 2-chloro-1-phenylethanols, precursors of optically active styrene oxides, can be prepared in very high yield and enantioselectivity by transfer hydrogenation of the corresponding α-chloroacetophenones with the chiral Rh complex Cp*RhCl[(*R*,*R*)-**11**] and TEAF.[13] The analogous Ru- based system derived from $[RuCl_2(\eta^6\text{-mesitylene})_2]$ and (*S*,*S*)-**11** allows for the highly effective hydrogenation of 2-cyano-, 2-azido- and 2-nitroacetophenone.[14]

The transfer hydrogenation of *t*-Boc-protected α-aminoketones provides an efficient method for the enantioselective synthesis of enantiomerically enriched aziridine and amino alcohols.[15] Reduction of α-hydroxyacetophenone to 1-phenyl-ethan-1,2-diol can be achieved in high ee without deactivation

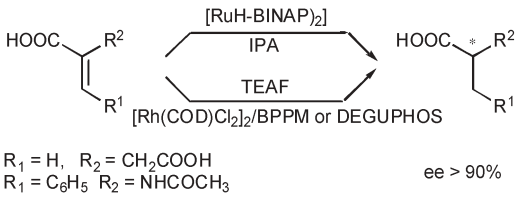


Scheme 10 Ee values (%) obtained in the asymmetric transfer-hydrogenation of functionalized ketones.

of the catalyst: the hydroxy group in the substrate in fact does not coordinate to the metal centre of the active catalytic species.[16] Optically active pyridyl alcohols, useful pharmaceutical intermediates and chiral auxiliaries in asymmetric synthesis, are likewise prepared from pyridyl ketones.[17] Noyori's catalyst is also effective in the transfer hydrogenation of benzoyltrimethylsilane.[18] The asymmetric reduction of benzil, a 1,2-diketone, gives almost quantitatively hydrobenzoin with excellent diastereomeric (*dl* : *meso* = 98.6 : 1.4) and enantiomeric purities (>99% ee). The reaction proceeds in step-wise fashion through a benzoin intermediate which, having a labile stereogenic centre, is converted to the major stereoisomer *via* dynamic kinetic resolution.[19a]

At low temperatures, unsymmetrically substituted aryl alkyl 1,2-diketones lead to optically active α-hydroxy ketones by preferential reduction of the less hindered keto group adjacent to the alkyl moiety in up to 99% ee and 89% yield.[19b] At high temperature, they produce preferentially *anti*-1,2-diols in up to 99% ee and 89% yield. The reduction of symmetrically substituted 1,3-diaryl-1,3-diketones affords diols in reasonably high de and ee (up to 90%) compared to unsymmetrically substituted 1,3-diketones (*i.e.* when alkyl and aromatic groups are present in the α-positions).[20]

Chemoselective transfer hydrogenation of β-ketoesters to the corresponding β-hydroxyesters can be carried out with $[RuCl_2(\eta^6\text{-arene})]$ and ephedrine or diamino-type chiral ligands. Higher enantioselectivities are achieved in the reduction of aromatic keto esters compared to aliphatic ones.[21] One major problem with Ru-complexes of chiral amino alcohols in the reduction of bifunctional ketones is the possibility of



Scheme 11 Selective H-transfer reduction of C=C of conjugated acid derivatives.

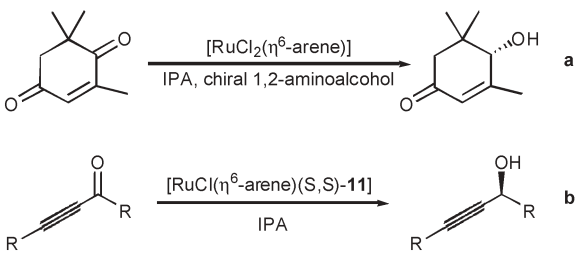
catalyst inhibition by coordination either of the reduction product[22] or even of the substrate in the case of β-diketones.[21]

Reduction of C–C multiple bond. Although transfer hydrogenation of **C=C** double bond is a thermodynamically favoured process even when alcohols are used as H-donors, only conjugated C=C double bonds are easily reduced. Conjugated acid derivatives, such as itaconic acid and α-acetamidocinnamic acid, are selectively reduced at the C–C double bond with ee higher than 90% either with $[RuH(BINAP)_2]PF_6$ in the presence of IPA as H-source[1a] or with rhodium complexes of chelating diphosphines like BPPM[23] and DEGUPHOS[1a] in the presence of TEAF (Scheme 11).

In the transfer hydrogenation of α,β-unsaturated carbonyl derivatives, a competition between vinyl and carbonyl group hydrogenation is expected. In general, the reduction proceeds preferentially at the carbonyl group producing the corresponding unsaturated carbinol. This is the case when aminoprolinate complexes of Ru[1a] and Rh[1a] are used as catalyst precursors, although the alcohols are obtained with modest enantioselectivity. It has been recently demonstrated, however, that with ruthenium amido complexes, the chemoselectivity can be completely reversed from C=O to C=C reduction, if the polarization of the C–C double bond is enhanced by the presence of additional electron-withdrawing substituents.[24]

The regioselective reduction of the oxo group of ketoisophorone proceeds with high stereoselectivity in the presence of Ru-catalyst with chiral amino alcohol ligands to give the 4-hydroxyisophorone in over 95% ee (Scheme 12a).[1a]

C≡C triple bonds are resistant to reduction and chiral propargylic alcohols are accessible in over 95% ee by transfer hydrogenation of conjugated ethinyl ketones with Noyori's catalyst (Scheme 12b).[1a] Regardless of the bulkiness of the R substituent bound to the carbonyl, the ee's are consistently high and both aryl- and alkyl ethinyl ketones serve as good substrates. Although terminal ethinyl ketones are not usable,



Scheme 12 Selective H-transfer reduction of C=O of conjugated carbonyl compounds.

their silylated derivatives are reduced easily under neutral conditions with a preformed catalyst. Notably, in the transfer hydrogenation of ethinyl ketones with a pre-existing stereogenic centre, diastereoface selection is determined solely by the chirality of the Ru catalyst.

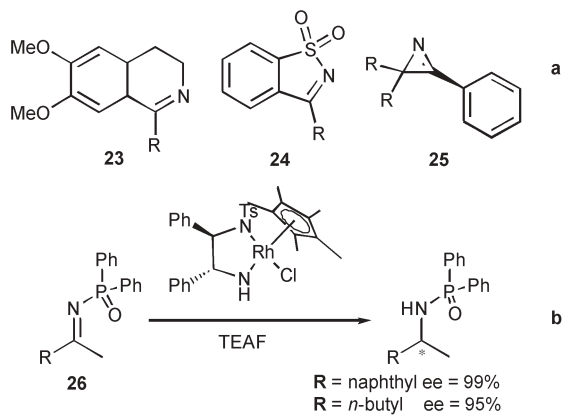
In IPA the ynone/ynol thermodynamic balance, which is the limiting factor of the yield, is shifted in favour of the reduced form. Thus the reaction is still synthetically useful even when run at a substrate concentration as high as 5 M. This reaction has been exploited in the stereocontrolled synthesis of a β-ionol glycoside.[1a] The reduction of conjugated ethinyl ketones proceeds in much lower yield and enantioselectivity in TEAF.

Reduction of C=N. The asymmetric transfer hydrogenation of the **C=N** double bond of imines holds great synthetic significance due to the importance of optically active amines as pharmaceuticals and agrochemicals.

In general, nitrogen containing functional groups are best reduced with TEAF than with IPA as H-donor. For instance, with TEAF, chiral tetrahydroquinolines and chiral sultams have been obtained from the corresponding imines **23** and **24**, respectively, with remarkably high ee's using ligand **11** either with $[Cp^*RhCl_2]_2$[1a] or with $[RuCl_2(\eta^6\text{-arene})]_2$[1a] as catalysts (Scheme 13a). The reduction with the rhodium complex proceeds at a considerably higher rate than those using Ru-based catalysts, although the latter ones provide consistently higher enantioselectivities.

The asymmetric transfer hydrogenation of dihydroquinoline intermediates has been successfully exploited in the key step of a total synthesis of morphine[25] and in the preparation of isoquinoline based pharmas.[26]

In general, acyclic imines are reduced in lower yield and ee than their cyclic counterparts. For *N*-substituted imines, this is due to the existence of different geometrical isomers which are reduced at different rates and with different selectivities. The interest of industry towards transfer hydrogenation is demonstrated by the development of catalysts for the transfer hydrogenation of phosphinylimines (R = Naphth and C_4H_9) with over 95% ee and 1000 h^{-1} TOF's.[27] The rationale for the high stereoselectivity resides in the large size of the phenylphosphinyl group, which may force the imine **26** (Scheme 13b) to



Scheme 13 H-transfer reduction of prochiral imines.

exist in just (or predominantly) one geometrical isomer. This group can be easily removed after reduction.

Chiral aromatic aziridines can be obtained from the asymmetric transfer hydrogenation of 2-arylazirines **25** (Scheme 13a) in IPA (TEAF is unsuitable as it causes decomposition of azirines) with the catalyst derived from $[RuCl_2(p\text{-cymene})]_2$ and chiral **14** (Scheme 7).[28]

In a control experiment it has been shown that with Noyori's catalyst, imines are much more reactive than ketones when reduced in TEAF. This feature has been conveniently exploited in the catalytic Leuckart–Wallach-type reductive amination of ketones. Primary amines can be synthesized by means of highly enantioselective catalytic hydrogen transfer reductive amination of aromatic ketones with ammonium formate.[29] The best enantioselectivities (up to 95% ee) are obtained with $[(Tol\text{-}BINAP)RuCl_2)]$ in NH_3/methanol at temperatures between 60 and 85 °C.

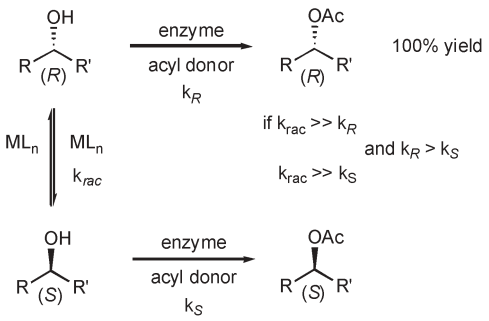
Kinetic resolution

Kinetic resolution. In spite of the spectacular results achieved by asymmetric chemocatalysis in the last decades, even nowadays in industry the method of choice for the production of enantiomerically pure compounds is resolution of racemic mixtures.

Conventional separation techniques can be favourably rivalled by kinetic resolution only if the reactivity of one of the two enantiomers towards an enantiopure reagent is large enough to allow for an efficient separation of the antipodes and if the resolving agent is used in a catalytic amount. A selectivity factor $E = k_R/k_S$ (k_R and k_S are the rate constants of each enantiomer towards the resolving agent) not lower than 25–30 is required to fulfil the first requirement.

A few Ru-based catalysts have shown a high efficiency in promoting the kinetic resolution of racemic secondary alcohols, especially those with high reduction potentials. They include Noyori's catalyst,[1c] the catalyst systems provided by $[RuCl_2(p\text{-cymene})]_2$ and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **13**[30] and catalyst **15**.[31] In general, enantioselectivities higher than 90% are achieved with α-tetralol scoring 99% ee. Noyori's catalyst has been successfully applied to the resolution of racemic 3-hydroxymethyl-1-tetralols and 3-hydroxymethyl-1-indanols which are potent substances acting on the central nervous system.[32]

Dynamic kinetic resolution (DKR). The major limitation inherent with kinetic resolution is that the maximum theoretical yield of a single enantiomer cannot exceed 50%. Because of this, a suitable procedure for the undesired enantiomer (distomer) to be racemized and recycled to resolution is mandatory for the economy of the process. If racemization can be coupled with kinetic resolution in such a way that both the processes can be run simultaneously, recycle is no more required and in principle 100% of the racemic mixture can be led to the desired enantiomer (eutomer). This approach, known as *dynamic kinetic resolution* (DKR),[33] relies on the fact that racemization is a thermodynamically favoured process due to the increase of entropy (Scheme 14).



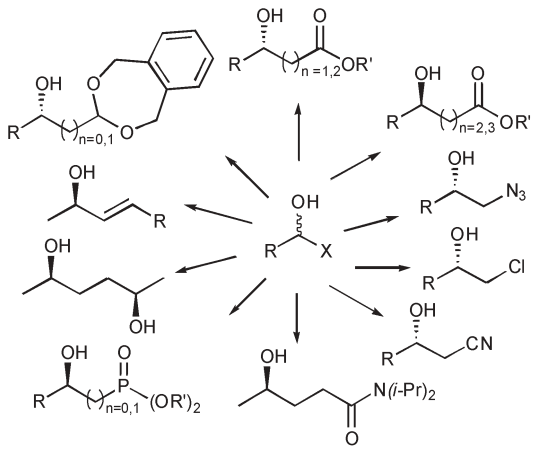
Scheme 14 Dynamic kinetic resolution.

An example of DKR which relies on purely chemical means is the hydrogen transfer reduction of 2-alkyl-1,3-dicarbonyl compounds with TEAF and Noyori's catalyst to give *syn*-2-alkyl-3-hydroxy ketones as the major products. In this case, racemization takes place *via* enolization at the configurationally labile stereocentre in position 2.[34]

As the hydrogen transfer reduction of ketones by IPA is a reversible process, the same catalysts used for the reduction of the carbonyl group can be exploited in the reverse reaction, *i.e.* the oxidation of carbinols to carbonyl compounds. By this way even primary alcohols can be converted into aldehydes.[35] This provides the rationale for the eutomer of a secondary carbinol to be obtained in more than 50% yield by coupling kinetic resolution of the racemic product with the H-transfer dehydrogenative oxidation of the distomer.

The *in situ* racemization of the distomer by a metal catalyst can be combined with the enzymatic resolution of the racemic alcohol. There are several examples where acylase-catalyzed resolution of secondary carbinols is coupled with Ru-catalyzed racemization of the unreactive enantiomer. Suitable catalysts for this process are $[(\eta^5\text{-indenyl})RuCl(PPh_3)_2]$, in the presence of triethylamine and molecular oxygen as the oxidant;[33] $(PPh_3)_3RuCl_2$ and $Ru(TsN(CH_2)_2NH)(p\text{-cymene})$ in combination with TEMPO as the oxidant;[33] $Cp^*RuCl(CO)_2$[36] (Cp^* = tetraphenyl alkylaminocyclopentadienyl) and, recent entry, the catalyst derived from $[RuCl_2(p\text{-cymene})]_2$, and *N,N,N,N*-tetramethyl-1,3-propanediamine.[37] In a particularly efficient case, the lipase-catalyzed resolution of aryl alkyl carbinols has been coupled with the Shvo catalyst (Fig. 1). Even if this complex, a dinuclear ruthenium hydride, is not among the most active racemization catalysts, it does not require a base for activation to catalysis. This fact has positive influence on the activity/stability of the enzyme and prevents undesirable side-reactions.[33]

Immobilization of the enzyme on suitable matrices provides robust acylases which can tolerate higher temperature and can be used in organic solvents without a dramatic decrease in activity. By assembling the proper combination of enzyme, metal catalysts, acyl donor and reaction conditions, a wide range of chiral substrates besides secondary carbinols has been successfully subjected to DKR. The list includes allylic alcohols, secondary diols, hydroxy acid derivatives, azido- and halo alcohols, hydroxy nitriles, δ-hydroxy esters, protected hydroxy aldehydes, α- and β-hydroxyalkanephosphonates, γ-hydroxy amides. These compounds are immediate precursors of a large range of chiral products of high synthetic value



Scheme 15 Range of compounds accessible through DKR of functionalized racemic alcohols.

such as epoxides, aziridines, β- and γ-amino alcohols, δ-lactones, β-halo alcohols, β-hydroxy acids, *etc.* (Scheme 15).[33]

When the resolving enzyme is a lipase only the enantiomer of (*R*)-configuration is accessible, in case simple secondary alcohols are resolved. Recently, however, an efficient (*S*)-selective DKR of secondary alcohols has been achieved at room temperature by combining the enzyme *subtilisin* with an aminocyclopentadienyl ruthenium complex as the racemizing catalyst.[38]

Enantiomerically pure primary and secondary amines are accessible through a DKR process which combines the enantioselective lipase catalyzed transacylation by ethyl acetate with the Shvo catalyst-mediated racemization of amines. Although in this case racemization and kinetic resolution are performed in separate steps, the procedure allows high functional group tolerance.[33]

The potential of dynamic kinetic resolution has been exploited for the first time in industry with the set-up in 2002 of a large scale process for chemoenzymatic DKR of secondary alcohols. The process, developed at DSM by Verzijl *et al.*, combines a modified Ru-Noyori type catalyst with an immobilized lipase (*Candida Antarctica* Lipase B; CALB).[33]

Catalyst evolution towards "Green" H-transfer processes

Modification of the parent structure of well established catalytic systems in order to improve catalyst performance and stability has been the subject of numerous recent efforts. Improving handling and separation of the catalyst from reaction products on the way to efficient recycling is a further topic of recent interest.

Scheme 16 summarizes some elaborations of Noyori's catalyst in this direction, but analogous modifications have been carried out on other successful catalytic systems. The ee's obtained in the reduction of acetophenone with each system are quoted.

Immobilization of Noyori's catalyst has been achieved by anchoring it onto a solid support, either inorganic or organic (**27**).[39] Depending on its nature, the organic matrix may or may not be soluble in the reaction medium, making the transfer hydrogenation a homogeneous or a heterogeneous process.

When the catalyst precursor is provided with one or more suitable side chains, it can be polymerized and cross-linked in the presence of a chiral molecule which mimics the substrate or the product. Selective removal of this template from the resulting polymer affords an immobilized catalyst with a cavity which acts as a centre of molecular recognition. The *imprinted* polymer[40] shows a significantly higher activity than control polymers without cavities and selectively reduces ketones whose structural features are similar to those of the imprinting template.

Core-functionalized dendritic ligands such as **28** have been synthesised by condensation of modified ligand **11** with Fréchet's polyether dendritic wedges.[41] In the transfer hydrogenation of acetophenone with TEAF, **28**, which is completely soluble in dichloromethane, shows high catalytic activity and enantioselectivity. It can be recovered through solvent-induced precipitation and it can be reused several times without loss of enantioselectivity and with moderate reduction of activity.

Noyori's ligand can be modified by introduction of imidazolium tags either at the complexed arene[42a] or at the tosyl group[42b] in order to immobilize the resulting catalysts **29** in ionic liquids. When acetophenone is reduced in ionic liquids with TEAF, the produced 1-phenylethanol is recovered by extraction with an organic solvent and the residual ionic liquid phase containing **29** is recycled and reused for the next reaction.

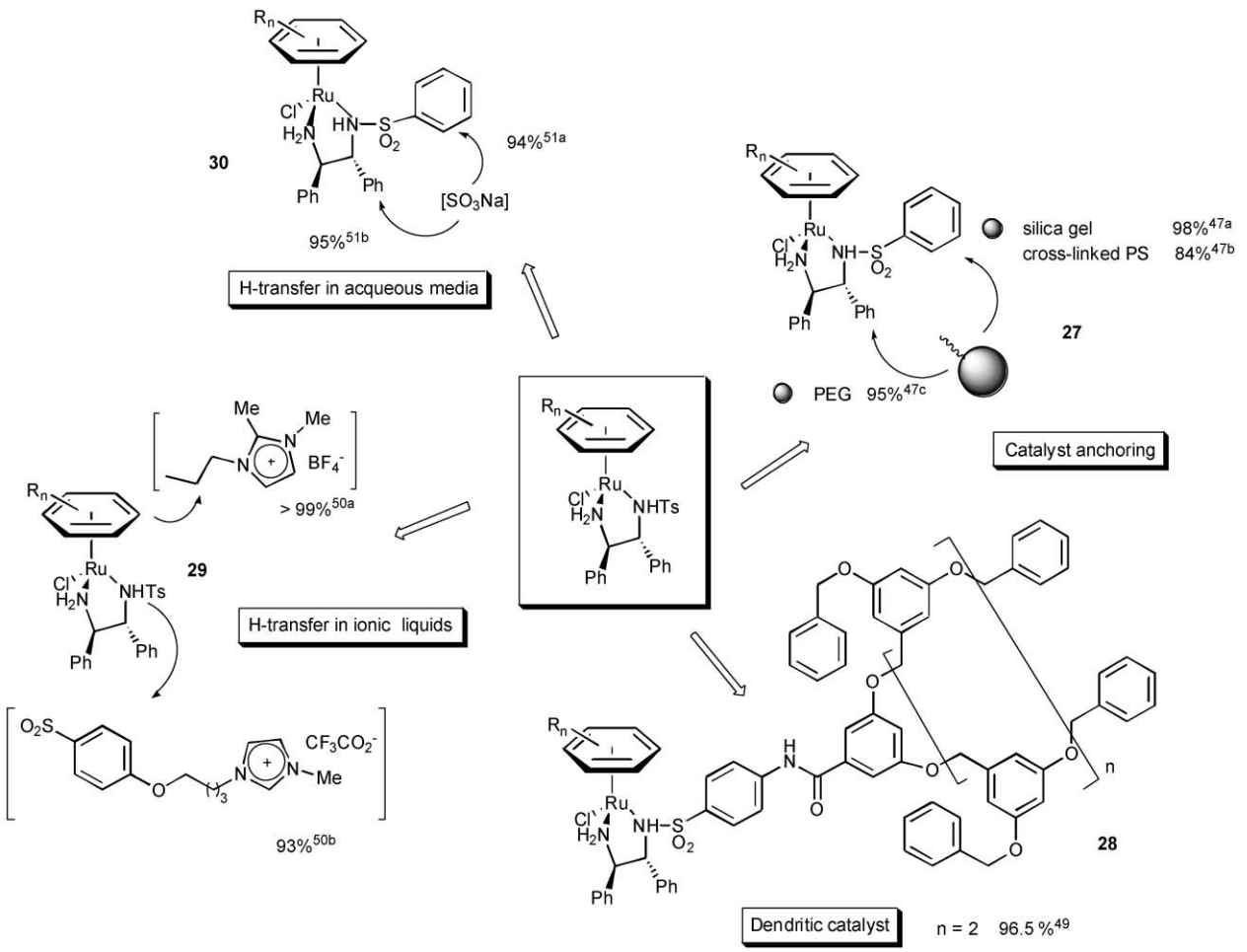
The quest for environmentally benign solvents has been addressed by preparing water-soluble versions of Noyori's catalyst **30**. They allow the transfer hydrogenation of aryl alkyl ketones to be run in aqueous media in over 95% ee, albeit at a lower rate than in the homogeneous phase. Water solubility is achieved by sulfonation either of both the phenyl substituents of the diamine ligand[43a] or of the tosyl group.[43b]

A water-soluble Ru complex of β-cyclodextrin-modified amino alcohol has been prepared. The β-cyclodextrin moiety plays an important role on the enantioselectivity through preorganization of the substrates in the hydrophobic cavity.[43c] Up to 97% ee and good to excellent yields have been obtained in the reduction of various ketones.

Recently it has been shown that when transfer hydrogenation of aromatic ketones is run in water with unmodified Noyori's catalyst and TEAF, two competing catalytic cycles seem to be operating at different pH. By adjusting the $HCOOH/NEt_3$ ratios in order to keep the solution pH in the range 5–8, high rates and high turnover numbers together with excellent ee values can be achieved.[44]

Concluding remarks

During the last few years hydrogen transfer reduction processes catalyzed by homogeneous transition metal complexes have grown up to become highly competitive with respect to hydrogenation with molecular hydrogen. These reactions can be run in quite mild conditions and are recommendable as synthetic tools due to their operational simplicity and high selectivity. A significant expansion of their field of application in the synthesis of fine chemicals can be



Scheme 16 Modifications of Noyori's catalyst aiming at recycling and *green* H-transfer processes. Ee (%) obtained in the reduction of acetophenone for each system is reported.

foreseen with the increased use of transition metal catalyzed reactions among synthetic chemists.

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